Tumor-like stem cells derived from human keloid are governed by the inflammatory niche driven by IL-17/IL-6 axis.

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Public Summary:
The fate of the stem cells, undergoing self-renewal or differentiation, is dependent on a specialized microenvironment or niche in which the cells reside . The stem cell niche encompasses all elements immediately surrounding the stem cells, including non-stem cells, the extracellular matrix (ECM), as well as soluble molecules present in the locale. Under homeostatic or physiological conditions, the extrinsic niche components or growth factors protect the stem cells from excessive proliferation by providing a balanced proliferation-inhibiting and proliferation-promoting signal. Meanwhile, the stem cells must periodically activate to produce specific lineage progenies for the regeneration or repair of tissues. Therefore, the maintenance of a steady state between stem cell quiescence and activity is the hallmark of a functionally normal niche, whereas the deregulation of niche signals may lead to the uncontrolled self-renewal and proliferation of the stem cells, thus contributing to the emergence of the so-called niche-generated diseases including pre-cancer and tumorigenesis. Keloid, a chronic inflammatory and fibro-proliferative disease, exhibits distinctive histological features characterized by a high density of mesenchymal cells, an abundant ECM stroma, a local infiltration of inflammatory cells including mast cells and lymphocytes, and a milieu of enriched cytokines, especially transforming growth factor-β1 (TGF-β1) and IL-6. Clinically, keloid behaves like a benign tumor as it continues to grow beyond the boundaries of the original wound margins, rarely regresses as observed in hypertrophic scars, and recurs at a high rate up to 80%. The benign but aggressive nature of the dermal tumor prompts us to hypothesize that stem cells may serve as primary source of multipotent cells to rapidly repopulate the wound site in response to exogenous insults, such as trauma, surgical injury, or infection. In addition, the unique microenvironment in keloid scars suggests that an altered or “pathological” niche exists in keloid that is contributory to the hyper-proliferative state of the stem cells, and consequently the sustained growth of the benign tumor. Therefore, keloids provide an ideal benign tumor model to study the role of stem cells and their special niche components in the development of the fibroproliferative disease. To this goal we have isolated and characterized a population of adult stem cells from the dermal layer of keloid scars, named keloid derived precursor cells (KPCs), and defined an essential inflammatory cytokine loop, IL-17/IL-6, constituting the “pathological” keloid niche that is capable of elevating the proliferation-promoting signal. Using KPCs transplanted in immunocompromised mice we generated a keloid-like tumor model that is driven by the in vivo inflammatory niche. Understanding how the inflammatory niche regulates tumor-like stem cell growth in keloid is critical in further elucidation of keloid pathogenesis and will open a new avenue for benign tumor stem cell research and ultimately, keloid therapies. Here we used keloid, an exuberant fibroproliferative dermal growth unique to human skin, as a model to characterize benign tumor-like stem cells and delineate the role of their “pathological” niche in the development of the benign tumor. We showed that keloid contains a new population of stem cells, named keloid derived precursor cells (KPCs), which exhibit clonogenicity, self-renewal, distinct embryonic and mesenchymal stem cell surface markers, and multipotent differentiation. KPCs display elevated telomerase activity and an inherently upregulated proliferation capability. The altered biological functions are tightly regulated by the inflammatory niche mediated by an autocrine/paracrine cytokine IL-17/IL-6 axis. Utilizing KPCs transplanted subcutaneously in immunocompromised mice we generated for the first time a human keloid-like tumor model that is driven by the in vivo inflammatory niche and allows testing of the anti-scarring therapeutic effect of antibodies targeting distinct niche components, specifically IL-6 and IL-17. These findings support our hypothesis that the altered niche in keloid scar, predominantly inflammatory, contributes to the uncontrolled self-renewal and proliferation of KPCs, supporting the rationale for in vivo modification of the “pathological” stem cell niche as a novel therapy for keloid and fibrotic diseases.

Scientific Abstract:
BACKGROUND: Alterations in the stem cell niche are likely to contribute to tumorigenesis; however, the concept of niche promoted

benign tumor growth remains to be explored. Here we use keloid, an exuberant fibroproliferative dermal growth unique to human skin, as a model to characterize benign tumor-like stem cells and delineate the role of their "pathological" niche in the development of the benign tumor. METHODS AND FINDINGS: Subclonal assay, flow cytometric and multipotent differentiation analyses demonstrate that keloid contains a new population of stem cells, named keloid derived precursor cells (KPCs), which exhibit clonogenicity, self-renewal, distinct embryonic and mesenchymal stem cell surface markers, and multipotent differentiation. KPCs display elevated telomerase activity and an inherently upregulated proliferation capability as compared to their peripheral normal skin counterparts. A robust elevation of IL-6 and IL-17 expression in keloid is confirmed by cytokine array, western blot and ELISA analyses. The altered biological functions are tightly regulated by the inflammatory niche mediated by an autocrine/paracrine cytokine IL-17/IL-6 axis. Utilizing KPCs transplanted subcutaneously in immunocompromised mice we generate for the first time a human keloid-like tumor model that is driven by the in vivo inflammatory niche and allows testing of the anti-tumor therapeutic effect of antibodies targeting distinct niche components, specifically IL-6 and IL-17. CONCLUSIONS/SIGNIFICANCE: These findings support our hypothesis that the altered niche in keloids, predominantly inflammatory, contributes to the acquirement of a benign tumor-like stem cell phenotype of KPCs characterized by the uncontrolled self-renewal and increased proliferation, supporting the rationale for in vivo modification of the "pathological" stem cell niche as a novel therapy for keloid and other mesenchymal benign tumors.
